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ARTICLE

Does mRNA SARS-CoV-2 vaccine detrimentally affect male fertility, as reflected by semen analysis?



BIOGRAPHY

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KEY MESSAGE:

According to World Health Organization reference ranges, 99% of the study cohort showed normal sperm concentration, motility and progressive motility and 100% normal morphology after their second COVID-19 vaccination. This suggests that COVID-19 vaccination is not detrimental to semen parameters and is safe to use in men wishing to conceive.

ABSTRACT

Research question: Does Pfizer's coronavirus disease 2019 (COVID-19) vaccination detrimentally affect semen analysis parameters?

Design: A prospective cohort study was conducted at a single large tertiary centre in Israel between February and March of 2021. Semen samples from 75 fertile men were analysed 1–2 months following their second dose of Pfizer's COVID-19 vaccine. The semen parameters were compared with the World Health Organization (WHO) reference ranges. The primary outcome was the percentage of abnormal semen parameters in those who were vaccinated, i.e. the rates of oligozoospermia, reduced percentage of motile spermatozoa and abnormal sperm morphology.

Results: The interval from the time of the second vaccination to the date of participation was on average 37 days, with most subjects describing either mild or no side effects after the first or second dose. The mean sperm concentration was $63.2 \pm 33.6 \times 10^6/\text{ml}$, with only a single participant (1.3%) with a sperm count of $12.5 \times 10^6/\text{ml}$, considered by the WHO to be oligozoospermic. The mean sperm motility percentage was $64.5 \pm 16.7\%$, with only a single man (1.3%) displaying reduced motility. No notable morphological abnormalities were observed. This constituted a lower percentage of abnormal semen parameters compared with the 5% rates reported in fertile men by the WHO.

Conclusions: The semen parameters following COVID-19 vaccination were predominantly within the normal reference ranges as set by the WHO and do not reflect any causative detrimental effect from COVID-19 vaccination. The results strengthen the notion that the Pfizer's severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is safe and should be recommended to men wishing to conceive.

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KEYWORDS

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INTRODUCTION

The 2019 novel coronavirus disease (COVID-19) is a highly infectious respiratory tract disease, first reported in December 2019 in Wuhan, Hubei Province, China, that has since spread globally. By March 2020, it was declared a pandemic by the World Health Organization (WHO) and has thus far affected tens of millions of people worldwide (Wiersinga *et al.*, 2020; Zhu *et al.*, 2020).

The ability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to cross the blood–testis barrier and affect male fertility is currently under dispute. A potential viral presence in the testes was suggested to be plausible due to the local expression of ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane protease serine 2) in Leydig cells (Chen *et al.*, 2020; Ma *et al.*, 2021; Wang and Xu, 2020). As such, a study by Li and colleagues had detected SARS-CoV-2 PCR-positive semen in 6 out of 38 patients (15.8%), and found histopathological signs of local elevated immune response and germ cell damage in testicular specimens from six deceased SARS-CoV-2 patients (Li *et al.*, 2020). Nonetheless, most studies published so far have found no viral traces in the semen of both men with active disease and those who have recovered, and a recent review determined that the likelihood of SARS-CoV-2 being present in the semen of COVID-19 patients is very small (Guo *et al.*, 2021; He *et al.*, 2021; Holtmann *et al.*, 2020; Kayaaslan *et al.*, 2020; Pan *et al.*, 2020; Paoli *et al.*, 2020; Song *et al.*, 2020).

Whether because of local infection in the testis, due to fever or through a general systemic inflammatory environment, a detrimental effect of COVID-19 infection on male fertility has been found (Gacci *et al.*, 2021; He *et al.*, 2021; Li *et al.*, 2020; Orvieto *et al.*, 2021). In the same previously mentioned study by Li and colleagues, the investigators compared semen analysis parameters in 23 COVID-19 patients with those of control participants and found that 39.1% of patients ($n = 9$) had oligozoospermia and 60.9% ($n = 14$) demonstrated a significant increase in leukocytes in the semen (Li *et al.*, 2020). Similar findings of abnormal semen analysis parameters were also reported in a recent study

by Gacci and co-workers. Within that cohort, as many as 25% (11 out of 43) men who had recovered from COVID-19 were oligo-crypto-azoospermic and 76.7% showed pathological concentrations of interleukin-8 in the semen (Gacci *et al.*, 2021). The authors of that study concluded that SARS-CoV-2 infection probably produces male genital tract infection, and men who have recovered should undergo a follow-up check on reproductive function.

The newly available mRNA SARS-CoV-2 vaccine from Pfizer has recently been evaluated in a large multicentre placebo-controlled randomized controlled trial. The vaccine comprises BNT162b2, a lipid nanoparticle-formulated nucleoside modified RNA encoding the SARS-CoV2 full-length spike protein, modified by two proline mutations. The two 30 µg doses have been shown to elicit high SARS-COV2 neutralizing antibody titres alongside high antigen-specific CD8+ and T-helper type 1 cell type CD4+ T cell responses. It was subsequently shown to be 95% effective in preventing SARS-CoV-2 infection a week following the second dose, with a favourable safety profile in a 2-month median follow-up time (Polack *et al.*, 2020).

Prompted by the aforementioned observations of abnormal semen parameters following SARS-CoV2 infection, unfounded claims in the popular media suggested a potential association between the SARS-CoV-2 vaccine and male infertility. This prospective study aimed to investigate the effect of BNT162b2 SARS-CoV-2 vaccination on the semen analysis parameters of fertile males. The initial hypothesis was that the vaccine would not elicit an adverse effect on semen parameters. This assumption was largely based on the relatively favourable safety profile of the vaccine, with Pfizer reporting that only 16% of individuals experienced mild to moderate fever after the second dose (Polack *et al.*, 2020).

MATERIALS AND METHODS

Study population and design

In this prospective study 75 fertile men younger than 45 years old were enrolled. Fertile men were considered to be those who had previously successfully impregnated their partners without the use of artificial reproductive technology. Recruitment was carried out by word of

mouth among medical staff in the Sheba Medical Center, Tel Hashomer Hospital and nearby hospitals, as well as being promoted via social media posts. The subjects volunteered freely and were not paid for participation. Men who were previously diagnosed with SARS-CoV-2 infection or were taking medications known to be detrimental to semen parameters were excluded.

Men recruited supplied a single sperm sample 1–2 months after the second dose of the vaccination by means of masturbation. At this time, they also filled in a brief questionnaire with information regarding their medical conditions and pernicious habits, as well as information regarding their reproductive history.

Specimen collection and handling

The participants were instructed to abstain from both intercourse and masturbation for at least 2–7 days before they supplied their sample. They were provided with a sterile cup and were asked to refrain from the use of lubricants. All samples were examined in the laboratory within 30–60 min from ejaculation by a single highly experienced embryologist (A.A.). The specimens were inspected noting the macroscopic and microscopic properties of the semen. Those parameters included liquefaction, viscosity, colour, volume, pH, sperm concentration ($10^6/\text{ml}$), motility (%), morphology (%) and vitality (%). These parameters were compared with the WHO semen analysis reference range in an attempt to ascertain whether the vaccine was affecting semen quality (Cooper *et al.*, 2010).

The evaluation of sperm concentration and motility was performed using a Makler counting chamber (Sefi Medical Instruments, Israel) according to the manufacturer's instructions. Evaluation of sperm morphology was conducted using pre-stained V-Sperm morpho slides (VitroMed, Germany) by smearing 10 µl of semen following liquefaction. The evaluation was performed at a final magnification of $1000 \times$ (Plan Apo 100 \times 1.45 Oil; Nikon, Japan) counting 200 cells. Spermatozoa were classified as having normal or abnormal morphological features according to WHO criteria (Cooper *et al.*, 2010). Vitality was analysed by eosin staining (Sigma, Merck, Germany). A smear of 10 µl of stock eosin mixed with 10 µl of semen was evaluated by counting at least 100 cells of red-stained

TABLE 1 SOCIODEMOGRAPHIC CHARACTERISTICS OF THE STUDY PARTICIPANTS (N = 75)

| Participants' characteristics | Results |
|---|-----------------------------|
| Age (years) | 38.6 ± 4.3, 38; 29–45 |
| Profession | |
| Doctor | 30 (40) |
| Other | 45 (60) |
| Body mass index (kg/m ²) | 26.7 ± 5.7, 25.7; 18.1–49.3 |
| Number of children | 2 ± 1.31, 2; 0–6 |
| Time since last birth (years) | 3.46 ± 3.01, 3; 0–12 |
| Smoking | 9 (12) |
| Yes | 66 (88) |
| No | 15 (20) |
| Social alcohol consumption | 60 (80) |
| Yes | 3 (4) |
| No | 72 (96) |
| Marijuana use | 37.2 ± 7.4, 37; 28–60 |
| Yes | 68 (90.7) |
| No | 3 (4) |
| Number of days from second dose of vaccine to participation | 2 (2.7) |
| Chronic medical conditions | 1 (1.3) |
| None | 1 (1.3) |
| Hypertension | |
| Crohn's disease | |
| Diabetes mellitus type 2 | |
| Hyperlipidaemia | |

Data are mean ± SD, median; range or n (%)

and unstained cells, at a final magnification of 400 × (Plan Apo 40 × 0.55; Nikon). For all the aforementioned evaluations (concentration, motility, morphology and vitality), two different specimens were examined from each sample and the average was recorded. All samples were discarded immediately after the laboratory evaluations.

Ethics

This study was approved by the ethics committee (Helsinki) of the Sheba Medical Center, Tel Hashomer (No. 8079-21-SMC) on 31 January 2021. Trial Registration: ClinicalTrials.gov identifier NCT04778033.

Statistical analysis

The most recent reference range for abnormal sperm count was defined by

the WHO in 2010 and consisted of the lower 5th percentile of sperm parameters in their cohort of fertile men (Cooper *et al.*, 2010). Those parameters included semen volume, sperm concentration, percentage of motile sperm, percentage of progressive motile spermatozoa, sperm morphology and vitality percentages. Based on this reference range, 5% of fertile men in the general population produce abnormal results. In order to investigate the effect of SARS-CoV-2 vaccination, a sample size of 75 participants was estimated to be sufficient to reveal a difference in abnormal sperm concentration (oligospermia) from a baseline of 5% to a proposed 15% after vaccination, with a type 1 error (alpha) of 5% and a type 2 error (beta) of 20%. This would represent a 10% increase in aberrant semen parameters, a milder

affect compared with that described following COVID-19 infection, with reported oligozoospermia rates of 25–40% (Gacci *et al.*, 2021; Li *et al.*, 2020).

Descriptive statistics were computed as mean, median and standard deviation (SD) for continuous variables and as frequencies for categorical variables. All statistical analyses were performed using IBM SPSS Statistics version 27 (IBM, USA).

RESULTS

The study population consisted of 75 fertile men with a mean age of 38.6 ± 4.3 who volunteered to participate in the study. TABLE 1 describes the sociodemographic characteristics of the participants. The majority of the subjects (90.7%) were healthy and had no chronic medical conditions. As medical staff were among the first to receive the vaccine, they were targeted earlier and comprised 40% of recruited men. Pernicious habits were rare: only 12% reported smoking, 20% social alcohol consumption and 4% marijuana use. The reproductive history of the subjects is also described in TABLE 1. The median number of children in the study group was two, and 80% of participants had successfully impregnated their partners within the previous 5 years.

The interval from the time of the second vaccination to the date of participation was on average 37 days. The majority of participants experienced (TABLE 2) either no side effects (32%) after vaccination, or only mild side effects such as fatigue (34.7%) and pain at the injection site (13.3%). Systemic effects were relatively rare: only 9.3% experienced fever and 8% experienced chills.

The sperm analysis parameters of the participants are described in TABLE 3,

TABLE 2 SARS-COV-2 VACCINATION SIDE EFFECTS REPORTED BY THE STUDY PARTICIPANTS COMPARED WITH THOSE REPORTED BY PFIZER

| Vaccine side effects | Fertile men (n = 75) (n, %) | Side effects reported by Pfizer ^a (n) |
|------------------------|-----------------------------|--|
| None | | |
| Fatigue | 24 (32) | Not reported |
| Pain at injection site | 26 (34.7) | 59 |
| Fever | 10 (13.3) | 78 |
| Chills | 7 (9.3) | 16 |
| Headache | 6 (8) | 35 |
| | 2 (2.7) | 52 |

^a In Polack *et al.* (2020).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 3 SPERM ANALYSIS PARAMETERS OF THE STUDY PARTICIPANTS COMPARED WITH THE WHO REFERENCE RANGE

| Semen analysis parameters | Semen parameters in the study cohort (n = 75) (mean ± SD, median; range) | Number (%) of specimens below the WHO 5th percentile | WHO reference 5th percentile (median) | WHO reference 50th percentile (median) |
|---------------------------------|--|--|---------------------------------------|--|
| Volume (ml) | 2.7 ml ± 1.53, 2.5; 1–9.5 | | | 3.7 |
| Sperm concentration (10 × 6 ml) | 63.2 ± 33.6, 60; 12.5–180 | 1 (1.3) | 15 | 73 |
| Motility (%) | 64.5 ± 16.7, 64; 6.5–92.2 | 1 (1.3) ^a | 40 | 61 |
| Progressive motility (%) | 53.8 ± 16.6, 53.5; 0–87.4 | 1 (1.3) ^a | 32 | 55 |
| Morphology (normal %) | 10 ± 3.4, 9.7; 3.4–17.5 | | 4 | 15 |
| Vitality (%) | 64.3% ± 10.9, 63.5; 8.5–87.8 | | 58 | 79 |

^a Same sample.

WHO, World Health Organization.

alongside a comparison with the WHO most recent reference range. The mean sperm concentration in the cohort was $63.2 \times 10^6/\text{ml}$, with only a single subject (1.3%) who had a sperm count of $12.5 \times 10^6/\text{ml}$, considered by the WHO to be oligozoospermic. The mean total motile percentage was 64.5%, with only a single participant (1.3%) displaying reduced motility, and no instances of progressive motility. No notable morphological abnormalities were observed.

DISCUSSION

This study was designed to identify potential detrimental effects of Pfizer's SARS-CoV-2 vaccine on male fertility. Although previous reports have demonstrated an increased risk of sperm count abnormalities among individuals with active SARS-CoV-2 and those who had recovered from it ([Gacci et al., 2021](#); [He et al., 2021](#); [Li et al., 2020](#)), the present study was not able to demonstrate any evidence of adverse effects on semen parameters following COVID-19 vaccination.

Semen analysis is routinely used in the workup of infertile couples. Threshold values to classify men as fertile, subfertile or infertile have varied significantly in different studies. In a study by Guzik and colleagues ([Guzick et al., 2001](#)) semen specimens from 765 infertile and 696 fertile couples were evaluated. The mean ± SD sperm concentration in the fertile group was $67 \pm 50 \times 10^6/\text{ml}$, the mean percentage of motile sperm was $54 \pm 13\%$ and the mean percentage of normal sperm morphology was $14 \pm 5\%$. In the past 40 years, the WHO has revised its lower reference values for normal semen analysis parameters five times. The most recent criteria published

in 2010 are based on semen specimens from 4500 fertile men with a time to pregnancy of less than 12 months. The lower boundary was determined by the 5th percentile of that group and is displayed alongside the results in [TABLE 3](#) ([Cooper et al., 2010](#)).

There is little evidence regarding the effect of different types of vaccination on semen parameters or male fertility. Recently, the authors' group reported on 36 couples undergoing consecutive ovarian stimulation cycles for IVF before and after receiving mRNA SARS-CoV-2 vaccine ([Orvieto et al., 2021](#)). No differences were observed between the IVF treatment variables, number of oocytes, fertilization rate or semen analyses. Moreover, a recently published research letter by Gonzales and co-workers found no significant decreases in any sperm parameter following two doses of COVID-19 mRNA vaccine in 45 men ([Gonzalez et al., 2021](#)). The current authors were unable to find any other study investigating the association between SARS-CoV-2 vaccination and male fertility. Although technologically different, a study by Catherino and collaborators found no effect on semen parameters, embryo quality or pregnancy outcome in anthrax-vaccinated US military service members ([Catherino et al., 2005](#)). Similarly, smallpox vaccination was not found to negatively affect male fertility in a large epidemiological study ([Jacobson et al., 2008](#)). In a study conducted on rodents no effect of human papillomavirus Gardasil vaccine on sperm parameters and reproductive performance was found ([Wise et al., 2010](#)).

With the exception of two specimens (2 out of 75, 2.7%), one oligozoospermic and one with reduced motility, none

of the vaccinated men in the study produced abnormal results. This constitutes a notably lower percentage of oligozoospermia than that reported in fertile men by the WHO (5%; [Cooper et al., 2010](#)), by Guzik and colleagues (around 5%), or in individuals with current or recovered SARS-CoV-2 infections (25–40%) ([Gacci et al., 2021](#); [Li et al., 2020](#)). Therefore, the values reported in the current study are those expected in the normal fertile population and do not reflect any causative detrimental effect of COVID-19 vaccination. As such, these results, combined with those previously reported by Gonzalez and collaborators ([Gonzalez et al., 2021](#)), suggest that vaccination is safe with no apparent detrimental effect on sperm parameters.

There are several limitations of this study. The participants were a relatively homogenic group of fertile men from high socioeconomic groups. Those who participated were only tested once after they were vaccinated and a subtle potential decrease in sperm parameters could be possible if a semen sample had been obtained before vaccination for comparison. This drawback was expected as the vast majority fertile men in Israel were swiftly vaccinated within weeks of vaccine availability, which did not allow consecutive testing. The rapid vaccine coverage also explains why the choice was made to compare the sperm parameters with the WHO reference range as opposed to a control group, which would have been very difficult to recruit under such time constraints. As the participants were followed up only 1–2 months after the second dose of the vaccine, long-term results have not yet been reported. Finally, only a small percentage of the subjects experienced systemic side effects such as fever (9.3%)

as a result of the vaccine compared with those tested by Pfizer (16%) (Polack *et al.*, 2020). This might be explained by the relatively younger age of the current cohort. Nevertheless, as a relatively large cohort of 75 participants is being reported, with only two borderline sperm specimens, and considering that spermatogenesis lasts on average 70–90 days, vaccination is unlikely to represent a clinically relevant effect within the time frame of the study.

CONCLUSION

A joint statement by the Society for Male Reproduction and Urology and Society for the Study of Male Reproduction advises that SARS-CoV-2 vaccination should be offered to men desiring fertility (*Joint Statement Regarding COVID-19 Vaccine in Men Desiring Fertility from the Society for Male Reproduction and Urology (SMRU) and the Society for the Study of Male Reproduction (SSMR) | ASRM*). False claims made by anti-vaccine activists suggesting a possible link between the SARS-CoV-2 vaccine and male infertility aim to incite fear and deter public opinion from vaccination, consequently jeopardizing the vaccination plan and the end of the pandemic. The current results refute such claims and strengthen the notion that the Pfizer's SARS-CoV-2 vaccine is safe and should be recommended to men seeking fertility seeking.

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